with Jennifer Levin Carter

The current state of molecular testing

Molecular testing has a long history. More recently this class of testing has become both more precise and better annotated. Data from such testing has found application is diverse areas, such as disease diagnoses, drug indications, and drug discovery and development. We contacted Jennifer Carter to address questions about the current state of molecular testing, and where she sees the field trending.

Dr. Carter is precision medicine entrepreneur and executive. She was the founder of N-of-One, Inc., a leader in oncology molecular decision support, recently acquired by Qiagen. Dr. Carter has a BS in Molecular Biophysics and Biochemistry from Yale University, and MPH from Harvard School of Public Health, an MD from Harvard Medical School, and is currently pursuing an MBA in the Executive MBA program at MIT.

Q Given that background, I'm going to ask Dr. Carter to address questions on her views on molecular testing as a foundation for precision medicine. Let's start with patient and physician engagement, and access to molecular testing. Dr. Carter, how do you see physicians using molecular testing data today? And how effective do you consider the current use of molecular testing?

A Thanks Tom. There is growing adoption by physicians of molecular testing for patients with certain types of cancer. But not necessarily across the board for all types of cancer.

Because more drugs have been approved, more targeted therapies have been approved, and more exposure for many physicians to this type of approach for their patients, we are seeing growth in the market.

There are still many barriers to getting patients tested. For example, many physicians still don't have good access to knowledge about the relevance of different tests and how to use the results of testing. The number of tests available is increasing which adds to this complexity. Lack of consistent reimbursement for Next Generation Sequencing and other molecular testing prevents patients from getting access to testing.

As we begin to learn more and gather more data about how testing can improve treatment, I believe this will help propel and grow the clinical uptake. There have been some significant examples in the market recently of the potential impact of NGS. A very

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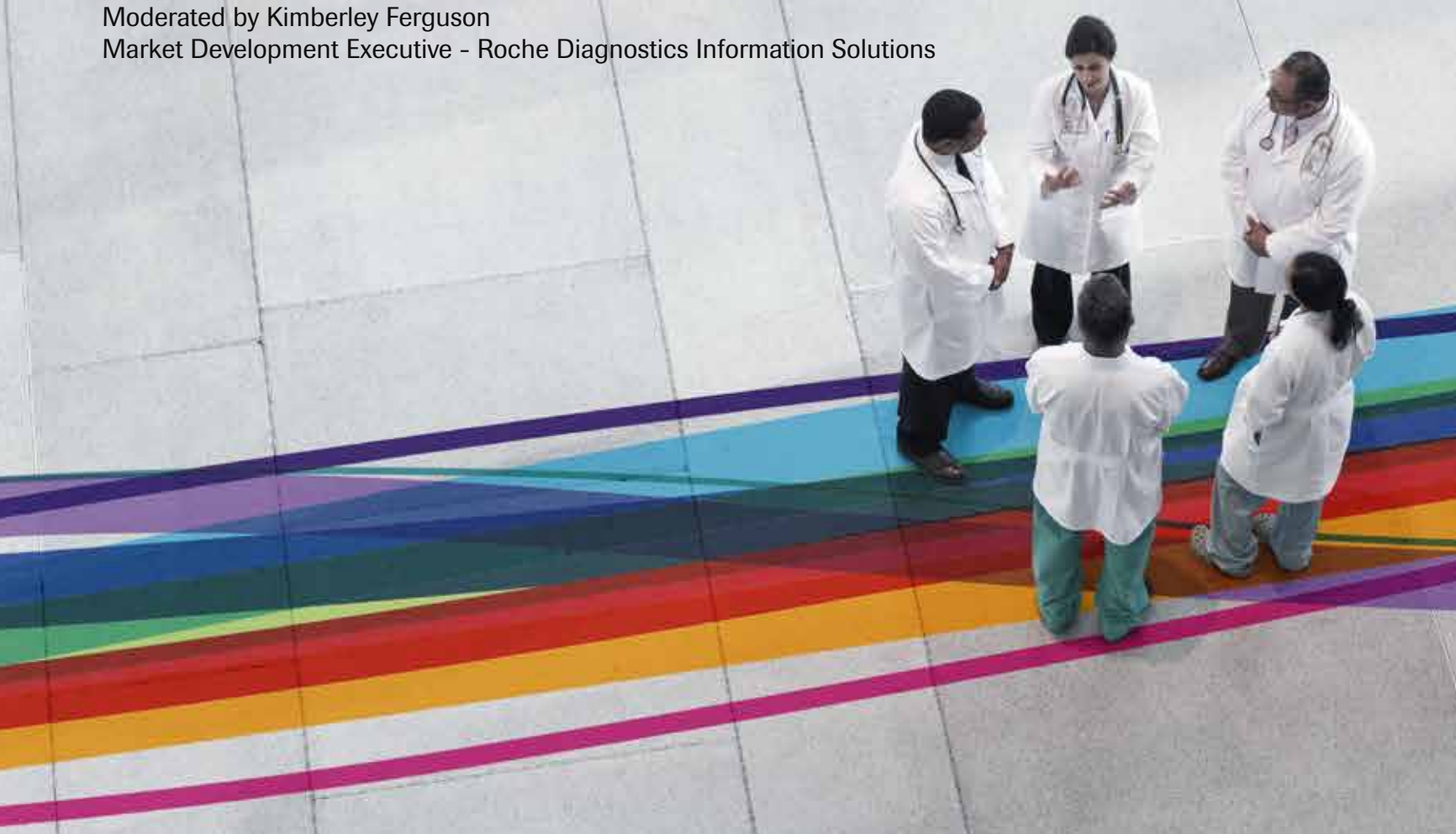
Wednesday, June 12th 2:45pm - 3:05pm
Precision Oncology - How the "End of Average" Transforms Clinical Decision Making
Speaker: Okan Ekinci, MD, MBA
Chief Medical Officer - Roche Diagnostics Information Solutions

Wednesday, June 12th 3:10pm -4:00pm
Panel Discussion - The Growing Role of Molecular Tumor Boards in Precision Oncology
Moderated by Kimberley Ferguson
Market Development Executive - Roche Diagnostics Information Solutions



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recent example is the approval of Loxo's NTRK inhibitor for all cancer types with NTRK alterations. This is a really exciting example of a true precision medicine, where a drug is approved to target a particular molecular driver, rather than just a particular tumor type based on organ of origin. And really, this is the foundation of what precision medicine is all about.

Q Thank you. And given that, what do you see are the challenges to adopting as quickly as you'd think it should be to select these other treatment strategies?

A One of the major challenges to adoption of molecular testing is lack of understanding of what the data mean, how to interpret the data, and thus how to use the data to impact intervention.

Data collected now is so complex. Understanding that data and the shades of gray of the data and how this data is linked to treatment is very complex. There's not always a 1:1 correlation, or a clear answer. Understanding of the data remains a challenge and a barrier for physicians in the application of it to clinical care.

The key is how you translate the information into treatment strategies. So is there an available clinical trial for the patient? Or a drug that's on the market, on-label or potentially off-label? And how do you get patients access to those therapeutic options? This all remains a challenge.

The other thing that we know and understand is that the biology is also very complicated. So just understanding one particular variant, one particular driver in a cancer, may stop tumor progression for a period of time, but the tumor cells are able to figure out a way to change in such a way that they can now become resistant to particular therapies.

We need to better understand the molecular biology, better assess multiple types of drivers in a particular tumor, and then be able to design better therapeutic strategy that targets these multiple drivers. This is very similar to the way that HIV has been treated and turned into a chronic disease. I think this is possible for other disease areas as well.

On the business side, there are also multiple challenges. There is still limited consistent reimbursement for molecular diagnostic testing. In part this is because there hasn't been enough outcome data to really demonstrate where and how the benefits of testing effect the patients in ways that can positively change outcomes while informing us about effective utilization. We have seen real progress with coverage of molecular testing in certain applications but much more is needed.

"EDUCATION IS A BIG VARIABLE TO BREAKING DOWN SOME OF THE BARRIERS TO ACCESS TO RELEVANT TREATMENTS"

Q And I'm curious, what improvements would you recommend to increase adoption, e.g., education or awareness? How do you see processes to improve uptake?

A Education is a big variable to breaking down some of the barriers to access to relevant treatments. Education for physicians, patients and payers – all stakeholders – is critical.

Also, using data to tell us how best to apply the molecular testing in ways that convince physicians to order the tests. Outcome studies will also help payers see the value of providing more reimbursement for NGS tests.

The immunotherapies are a good example – we know that there are certain patients that have phenomenal response to immunotherapy, while others may not respond at all. And the predictive markers and biomarkers that we have currently are not reliable enough to be able to tell us that a patient will or will not respond to a particular immunotherapy. These are some of the complexities in terms of driving widespread adoption.

Q That's actually a good segue. Maybe you could give us a brief overview of the different types of molecular testing currently in use?

A My focus to date has been in oncology. By and large, the greatest utilization and uptake over the last five years has been next generation sequencing. This testing analyzes the DNA for alterations that may provide clues for particular drivers of the tumor, and therefore particular treatment strategies that may be relevant. In NGS, different size panels that test different number of genes, disease specific panels that focus on key alterations by cancer type, have been developed.

An older type test called immunohistochemistry, IHC, is used for measuring PD-L1, a marker for some of the checkpoint inhibitors. That is a test being done more regularly. It's not the most reliable biomarker for determining whether a patient will be a responder to a checkpoint inhibitor. Other tests that may be included in a next generation sequencing panel, like tumor mutational burden, markers of microsatellite instability, these types of tests are also helpful as they can give a clue as to whether a patient will be responsive or not to immunotherapies.

We'll see an evolution of more use of other types of tests in the clinic: there will be greater application of transcriptomics, proteomics, and ex vivo testing of the tumors.

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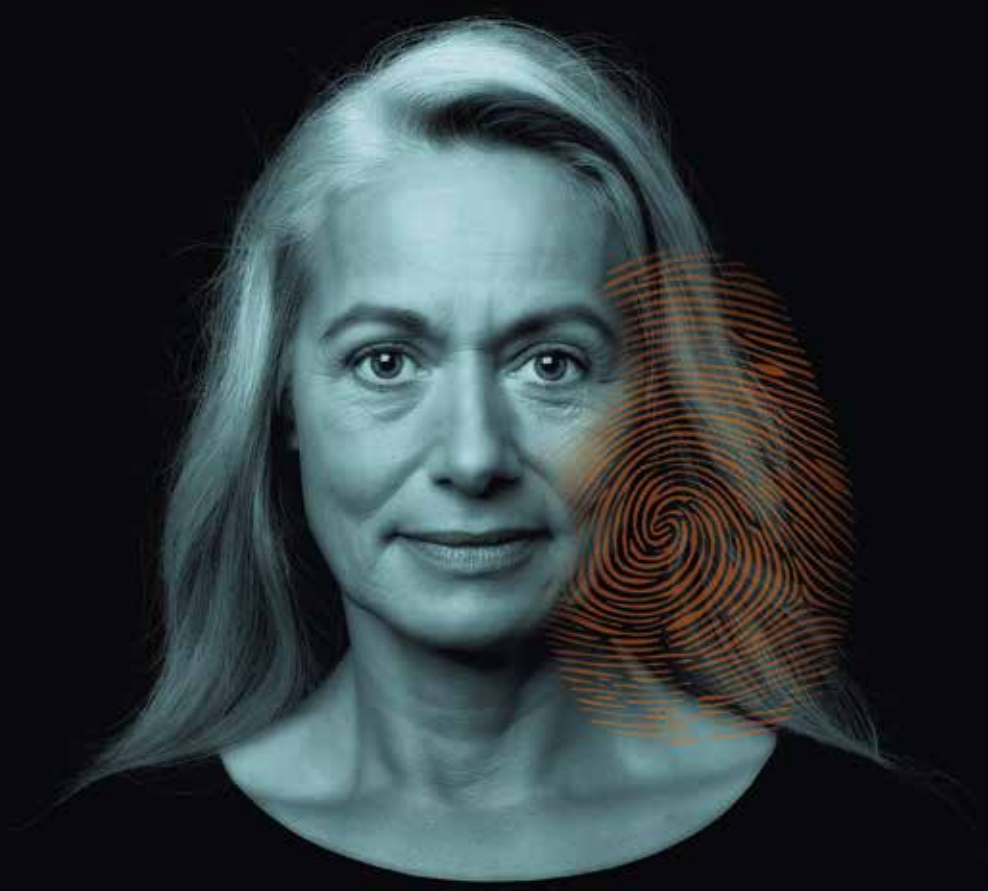
Expanding precision medicine



We believe that medicine will become more precise. However, medicine today is generally based on a "one-size-fits-all" practice, and where targeted therapies are possible, it is impractical to scale.

The goal of expanding precision medicine is to provide the right treatment at the right time for every patient. Tailoring treatment starts with a highly-specific diagnosis without unwarranted variation. Based on data integrated from existing sources, adding genomics and radiomics enables a holistic understanding of the individual. These unique characteristics steer the personalization of treatment. A precise understanding of a patient's condition is the most effective approach to deliver outcomes favorable to all stakeholders.

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Ex Vivo testing may be particularly important to assess efficacy of immunotherapies, because the tumor microenvironment is so important for driving resistance to immunotherapy or resistance to immune response..

So I think there's a lot of evolution in the somatic oncology. In germline, there's definitely more interest in testing for inherited risk of cancers. And certainly we have seen more adoption in the industry for germline testing for other disease areas beyond oncology as well as for prevention.

These are some of the areas where precision medicine is really going to grow, and it's starting to become more and more a part of clinical care.

Q Excellent. What advice would you provide physicians about using molecular testing in their precision medicine practice in general?

A The advice that I'd provide is that precision medicine can be highly, highly valuable to patients, both in terms of driving decisions around treatments, but also in better understanding their disease.

For germline diseases or for inherited diseases, it can be very helpful for patients to have conversations about screening and about disease prevention. That is critically important – we don't talk enough about this in medicine, where we can intervene early through screening and prevent people from developing disease, rather than being in the position of having to treat a person when they become sick. This is a very complex area but the potential impact is significant, so these issues need to be addressed.

At the end of the day, there's so much value for patients and their families around better understanding their disease. Thus, I believe, that these tests will become a really critical component of preventive care and treatment for patients with many, many types of underlying illness.

Q I have just heard people starting to talk now about preventive medicine in this regard, so that's a very good point. Thank you for raising that.

Do you see a distinction between how doctors use molecular testing in clinical trials, versus how they use them in practice – I mean with patients they're seeing on a regular basis.

A That's a hard question to answer because many of the clinical trials are now in oncology and require an associated biomarker test. The FDA in many cases is mandating that many of the new drugs have a companion biomarker. Many companies are looking for predictive markers for immunotherapies. New classes of therapeutics, like CAR-T cells, ASOs, are developed, in particular, because the etiology of a disease is an underlying genetic alteration.

In the clinic, access to testing depends on so many variables – where patients are getting treated, physician awareness, patient awareness, access to therapies, access to trials, and reimbursement.

"MACHINE LEARNING AND AI ARE GOING TO BE GREAT ENABLERS IN CLINICAL PRACTICE"

Q Thank you. Let's move on to a couple of questions on how you see the future playing out in AI and machine learning, what have you.

Eric Topol has a new book out on how AI can do more than enhance diagnoses and treatment. He foresees that AI could potentially free up doctors from time consuming tasks like taking notes and reading scans and what have you. And that would allow doctors to spend more time connecting with their patient.

Could you please tell us what you think of that, and how healthcare providers might be empowered to engage each other more directly using AI as a tool.

A Topol wrote a great piece in Nature Medicinel in January as well (High-performance medicine: the convergence of human and artificial intelligence), which was great review of many of the potential applications for AI in healthcare. There are many great examples in which the technology will enable more accurate diagnostics, as well as potential interventions, as so much data and information can be processed so quickly.

Machine learning and AI are going to be great enablers in clinical practice. And certainly in precision medicine, they're going to be real enablers of the testing and interpretation. They can review and parse more literature and data faster than a person, and make relevant information available for human review.

In areas like radiology, there is lots of data, AI can be used in ways that the human brain and a human eye is challenged – that opens up fantastic opportunities to really take clinical practice to a new level.

However, certainly in precision medicine and likely in most other disease areas, and Topol's article states this as well, at least for now, scientists and clinicians are really critical for the accurate interpretation of genomic data and the creation of the right treatment strategy based on the data.

And so while AI, machine learning, and other software will be a great enablers, these tools are not going to replace the critical need for the trained physicians or scientists, to be able

to really understand where the shades of gray are in the data, and how the data can really be applied.

Another point that Topol calls out in his article is that for AI/ML to be powerful, the input data must be of very high quality and highly correlated with the question being asked. It is critical to have the right data inputs to develop and train the algorithms so that the output is relevant and has very accurate predictive power.

These are a few of the challenges, but I absolutely think that AI will create new efficiencies, new productivity, new workflow improvements, and that the results can really drive continued innovation.

Q How do you think that the healthcare providers and the patients will be able to engage these tools in the future? Would that be through laptop screens, cellphones? How do you see that – for example, a doctor or a genetic counseor sitting down with a patient and discussing results that have been processed through AI?

A This is going to be a big challenge, right? But I mean, we're already seeing the use of more wearable technologies that are collecting data all the time, and that enable ongoing monitoring and data collection from people throughout the day in their home and work environments.

FDA is talking about collecting real world evidence for many clinical trials, so this will become part of the paradigm. There is a growing opportunity to bring wearables and digital technologies to patients' so we can monitor, collect, and analyze their health data remotely.

While more data offers a phenomenal opportunity, the challenge is going to be how clinicians will be able to manage all this data. How does it all get interpreted and processed? How do you incorporate this data in a way that it doesn't become overwhelming and so complex that most physicians cannot or do not use it effectively?

These are just some of the challenges that need to be addressed. But the potential impact, the ability to drive efficacy, efficiencies and scale and productivity and more knowledge, provides incredible opportunity to advance clinical care.

Q Thank you. And last question. Could you share what your vision is for precision medicine, or any other areas you would like to address?

A I've been in the precision medicine space now for over l0 years, and I have really seen that, for patients in oncology in particular, the insights into potential treatment options that can come from the molecular profiling of a patient's tumor are truly impactful. This can also be true of a germline inherited risk test. With the application of NGS, many new therapies and classes of therapies have been developed that have had a significant impact on patients.

We have seen many new treatments come to market that provide improved efficacy and have helped some people live longer often with reduced toxicity. These new tests can also suggest that certain drugs are not going to be effective. The opportunity to apply the data to patient care creates a phenomenal opportunity to continue to drive drug development and clinical care in different ways.

There are some definite challenges that we need to address: the development of new technologies for better understanding of the biology, interpretation of the data, creation of better opportunities for education and access for physicians and patients, changes in drug pricing, reimbursement and more insight into outcomes. But the overall power of precision medicine is phenomenal. And my vision for the future is that all patients with cancer and with other diseases will get profiled earlier in their disease, and have better access to treatment and prevention. ■

Reference

1. High-performance medicine: the convergence of human and artificial intelligence, Eric J. Topol , Nature Medicine, volume 25, pages 44–56 (Review Article, 07 January 2019)

Jennifer Levin Carter, MD, MPH, MBA'19, is at Integral. Dr. Carter is a Precision Medicine Entrepreneur and Executive. She was Founder, President and Chief Medical Officer of N-of-One®, Inc., the global leader in oncology molecular decision support, acquired by Qiagen in January, 2019. Dr. Carter has a passion for finding solutions to improve patient care. Her particular focus has been the development and delivery of solutions to enable greater patient and physician access to novel diagnostics and therapeutic strategies. Since 2012, she has participated as a regular presenter, expert panelist, or moderator at industry conferences, events, and symposia and serves on multiple industry advisory boards. Prior to founding and leading N-of-One® in 2008, Dr. Carter spent eight years as an Investment Consultant specializing in biotechnology and life sciences investments. After obtaining her MD, Dr. Carter practiced internal medicine at Mount Auburn Hospital in Cambridge, MA.

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